Journal of Pharmacreations

PharmaCreations

Pharmacreations | Vol.3 | Issue 1 | Jan- Mar- 2016

Journal Home page: www.pharmacreations.com

Research article ***Open Access***

Formulation and evaluation of metformin and rosuvastatin bilayered tablets

M. Sambasiva Rao, A. Sunil Kumar Reddy, A. Ashok Kumar

Professor & HOD OF Vijaya College of pharmacy, Munaganur (village), Hayathnagar (Mandal), Ranga redy (District), Pin-501511.

***Corresponding author: A. Ashok Kumar**

Email: ashok576@gmail.com

ABSTRACT

The Bilayered tablets containing Metformin SR and Rosuvastatin IR were successfully prepared by direct compression method and wet granulation method respectively. Various formulations were prepared and evaluated with an aim of presenting Metformin as sustained release and Rosuvastatin as immediate release for improving the patient's compliance. The physiochemical evaluation results for the granules of all trials pass the official limits in angle of repose, compressibility index. The prepared blend for IR layer tablets and SR layer tablets were also maintained the physiochemical properties of tablets such as thickness, hardness, weight variation, friability. The optimized formulation F5 in IR formulations contains the average thickness of 2.98mm, average hardness of 5.9 kg/cm^2, average weight of 152mg, friability of 0.36%. The optimized formulation F4b in SR formulations contains the average thickness of 5.9 mm, average hardness of 8.4 kg/cm^2, friability of 0.30%.The F4b formulation which releases the Metformin in sustained manner in 1st hour it releases 26.58% but the remaining drug release was sustained up to 12 hours and Rosuvastatin immediate release F5 formulation showed 100.61 % drug release within 60 min. With the data of kinetic analysis, F4b formulation showed best linearity in Higuchi's Equation plot indicating that the release of drug from matrix tablet follows Non Fickian diffusion.The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations.

Keywords: Direct Compression Method, Wet Granulation Method

INTRODUCTION

Multilayer tablets

Multilayer tablets are tablets made by compressing several different granulations fed in to a die in succession, one on top of another, in layer. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for 2 or 3 layers. More are possible but the design becomes very special. Ideally a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

Advantages of Multilayer tablets

1. Incompatible substances can be separated by formulating them in separate layers as a two-

2. layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two
3. Two layer tablets may be designed for sustained release –one layer for immediate release of the drug and the second layer for extended release, thus maintaining a prolonged blood level.
4. Layers may be colored differently to identify the product.

Certain single layer or unit tablet presses are equipped with two pre-compression stations prior to the final compaction. This provides high speed production by increasing dwell time of the material under pressure making for harder, denser tablets

The goal to designing bilayer tablets

- Controlling the delivery rate of either single or two different API'S.
- To separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property).
- For the administration of fixed dose combinations of drugs, Prolong the drug product life cycle**,** buccal /mucoadhesive delivery systems, manufacture novel drug delivery systems such as chewing device and floating tablets for gastro-retentive drug delivery systems.
- To adapt the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable / erodible barriers for controlled release.
- Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. In which the one layer is formulated to obtain immediate release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second layer is a controlled release, which is designed to maintain an effective plasma level for a prolonged period of time. The pharmacokinetic advantage relies on the fact that drug release from fast releasing layer leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining layer.

AIM AND OBJECTIVE OF PRESENT STUDY

The aim of the present study was to design and evaluate bilayer tablets ofMetformin and Rosuvastatin. An attempt was made to develop bi-layer tablet suitable for delivering different drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as sustained release of drug which gives effect of drug for sufficient long time and reduce frequency of dose.

Objectives

- To optimize the concentration of Polymer for sustaining layer, Metformin.
- To select and optimize the concentration of disintegrant for immediate release layer, Rosuvastatin.
- To select the suitable filler to produce the bulkiness and desired weight.
- To select the dissolution media, by performing solubility studies.
- To perform the drug – excipient compatibility studies as per ICH guidelines

METHODOLOGY

Preparation of linearity plot of Rosuvastatin in 0.1N HCl

Preparation of 0.1N HCl

Take 8.5ml of HCl in distilled water and make up to 1000ml with distilled Water to get 0.1N HCl

Determination of λ max of Rosuvastatin in 0.1N HCl

Rosuvastatin was dissolved in 0.1N HCl and the λ_{max} was obtained at 248 nm against the blank primary stock solution concentration of Rosuvastatin 1000 µg/ml was prepared. All measurements were made at room temperature.

Standard Stock solution

100 mg of Rosuvastatin was dissolved in 100 ml 0.1N Hcl to give a concentration of (1000 µg/ml)

Scanning

From the stock solution 100µg/ml was prepared in 0.1N HCl and UV scan was taken between 200 to 400 nm. The absorption maximum was found to be 248 nm and was used for the further analytical studies.

Calibration curve of Rosuvastatin in 0.1N HCl

The standard solutions were prepared by proper dilutions of the primary stock solution with absolute 0.1N HCl to obtain working standards in the concentration range of 5-35µg/ml of pure sample of Rosuvastatin. The concentration of Rosuvastatin present in the microspheres was obtained from the calibration curve.

Construction of Standard Graph of Metformin (0.1 N Hcl)

Preparation of stock solution

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Few ml of water was added to dissolve the drug and volume was made up to 100 mL with 0.1 N HCl . The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'.

Preparation of working standard solution

From this stock solution 10ml was taken and diluted to 100 mL with 0.1 N HCl which has given the solution having the concentration of 100 mcg/mL.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentrations of metformin (2-10mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (233nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Construction of Standard Graph of Metformin (pH6.8 buffer)

Preparation of stock solution

Accurately weighed amount of 100 mg was transferred into a 100ml volumetric flask. Few ml of water was added to dissolve the drug and volume was made up to 100 mL with pH6.8 buffer. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'.

Preparation of working standard solution

From this stock solution 10ml was taken and diluted to 100 mL with pH6.8 buffer which has given the solution having the concentration of 100 mcg/mL.

Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentrations of metformin (2-10mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (233nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Formulation of Bilayer Matrix Tablet (Sustained Release Layer)

The bilayer tablet was prepared by wet granulation method.

Sieving

The active ingredient was passed through the sieve#40 followed by the other ingredients were passed the same sieve.

Dry mixing

Metformin, guar gum, xanthum gum, Micro crystalline cellulose were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients with the drug.

Preparation of binder solution

- Meglumine
- Water

Weigh Meglumine accurately and it is mixed with water to form a paste is used as binder solution and kept separately.

Granulation

The binder solution was added slowly to the dry mixed ingredients with constant mixing till to get solid mass to form uniform and optimum granules.

Drying

Then the wet granules were dried in trays and pass the air for drying .Samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content.

Sieving

The dried materials were passed through the sieve#20

After sieving dry granules were lubricated using Mg.stearate and Aerosil. After lubrication granules were sent to compression. Metformin layer was compressed using 12mm round punch.

Composition OF SUSTAINED RELEASE LAYER

Table no: 1 formulation table for sustained release layer

Ingredients(mg)	F_{1a}	F_{1b}	F_{2a}	F_{2b}	F_{3a}	F_{3b}	F_{4a}	F_{4b}
Metformin	500	500	500	500	500	500	500	500
Xanthum Gum	142.5	--	190	--	237.5	--	285	--
Guar gum	--	142.5	--	190	--	237.5	--	285
Meglumine	28.5	28.5	28.5	28.5	28.5	28.5	28.5	28.5
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg.Stearate	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5
Aerosil	4.75	4.75	4.75	4.75	4.75	4.75	4.75	4.75
Total weight	950	950	950	950	950	950	950	950

Direct compression for immediate layer

All the ingredients were passed through sieve and mixed in a motor and pestle for 30min for uniform mixing. The addition of ingredients was done in a geometrical manner. Then the Rosuvastatin layer was compressed using 8mm round punch.

COMPOSITION OF IMMEDIATE RELEASE LAYER

Table no: 2 formulation table for immediate release layer

Ingredients(mg)	F_1	F_2	F_3	F4	F5	F6	F7	F8	F9
Rosuvastatin	10	10	10	10	10	10	10	10	10
CCS	3.75	--	--	7.5	11.25	--	--	--	--
SSG	--	3.75	--	--	--	7.5	11.25	--	--
CP	--		3.75	--	--	--	--	7.5	11.25
PVP K30	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
MCC	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium Stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Talc	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total weight	150	150	150	150	150	150	150	150	150

Bilayered tablet punch

After the batch was optimized in both immediate release layer and sustained release layer. The optimized batch in both was compressed by using same ingredients.

RESULTS AND DISCUSSION

Preformulation studies

Preparation of standard calibration curve of rosuvastatin

Table No: 3 concentration and absorbances of rosuvastatin in 0.1N Hcl

S.No	Concentration	Absorbance at 248nm
1	5	0.071
2	10	0.134
3	15	0.201
4	20	0.261
5	25	0.322
6	30	0.382
7	35	0.443

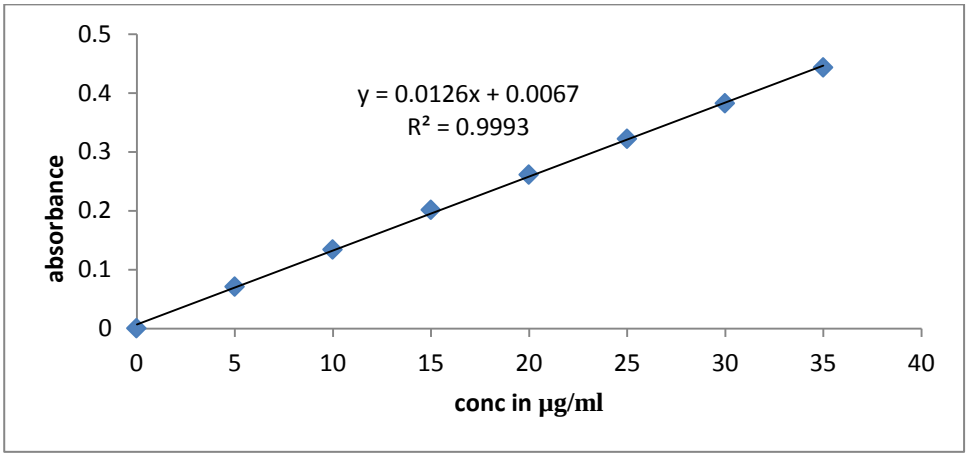

FIG NO: 1 - calibration curve of rosuvastatin

Standard Graph of Metformin (0.1 N HCl)

The standard graph of Metformin has shown good linearity with R^2 values 0.9988 in 0.1 N Hcl and which suggests that it obeys the "Beer-Lambert's law"4

Table No: 4

Concentration	Absorbance at 233nm
0	0
2	0.202
4	0.395
6	0.558
8	0.745
10	0.912

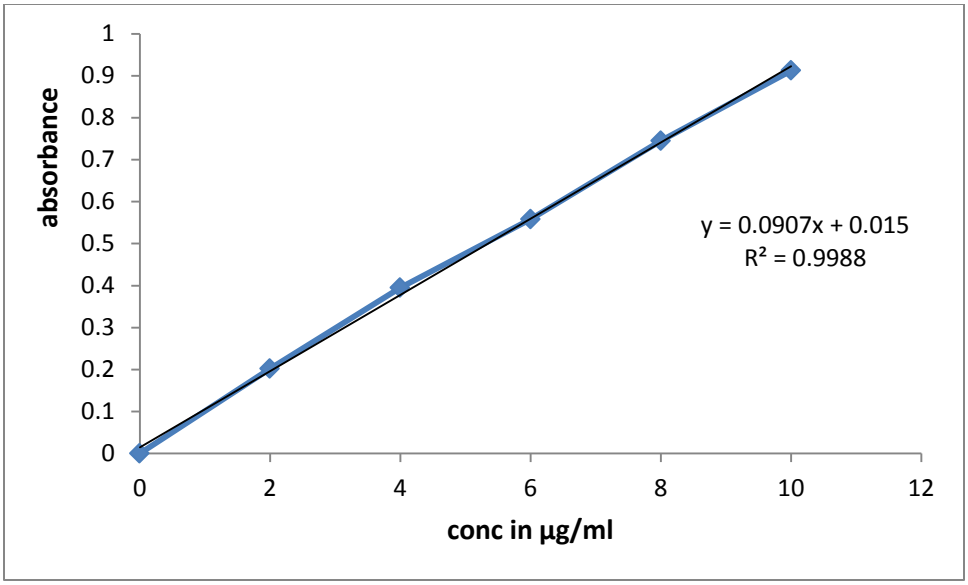

Fig no:2 calibration curve for Metformin in 0.1N Hcl at 233nm

Standard Graph of Metformin in 6.8pH phosphate buffer

The standard graph of metformin has shown good linearity with R^2 values 0.9986 and, which suggests that it obeys the "Beer-Lambert's law".

Table No- 5

Concentration	Absorbance
0	0
2	0.156
4	0.290
6	0.419
8	0.580
10	0.718

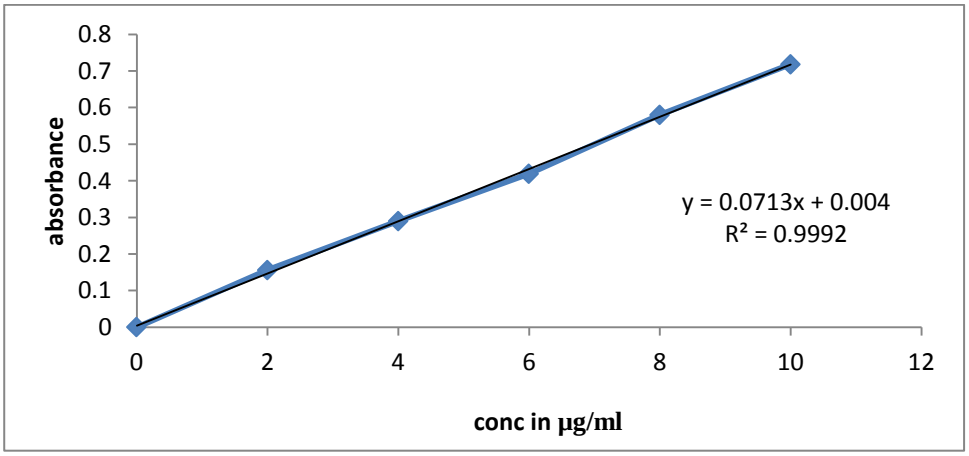

Fig no:3 calibration curve for Metformin in 6.8pH phosphate buffer at 233nm

DRUG AND EXCIPIENT COMPATIBILITY STUDIES

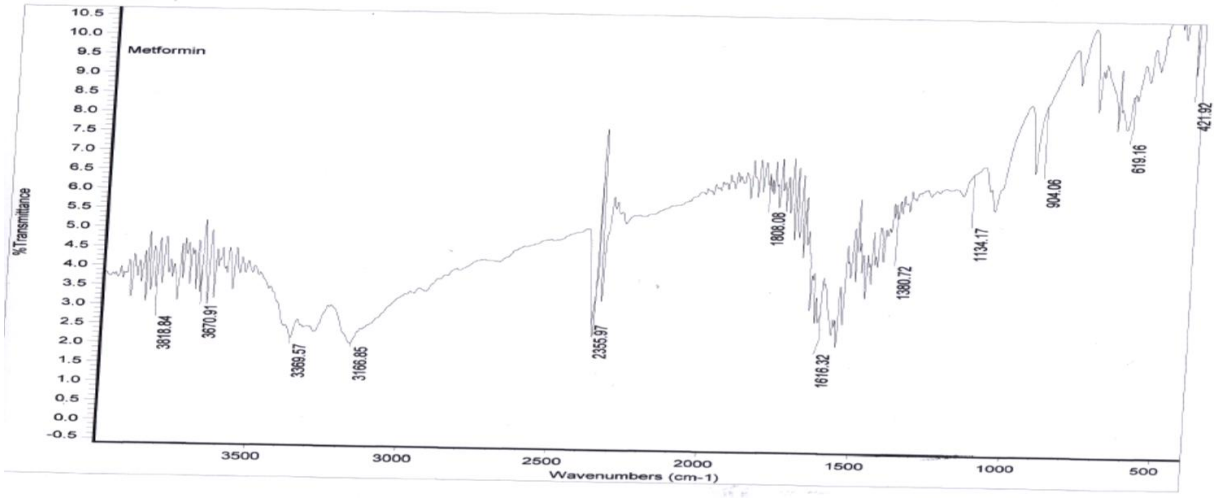

Fig No: 4 FTIR Spectra of Metformin pure drug

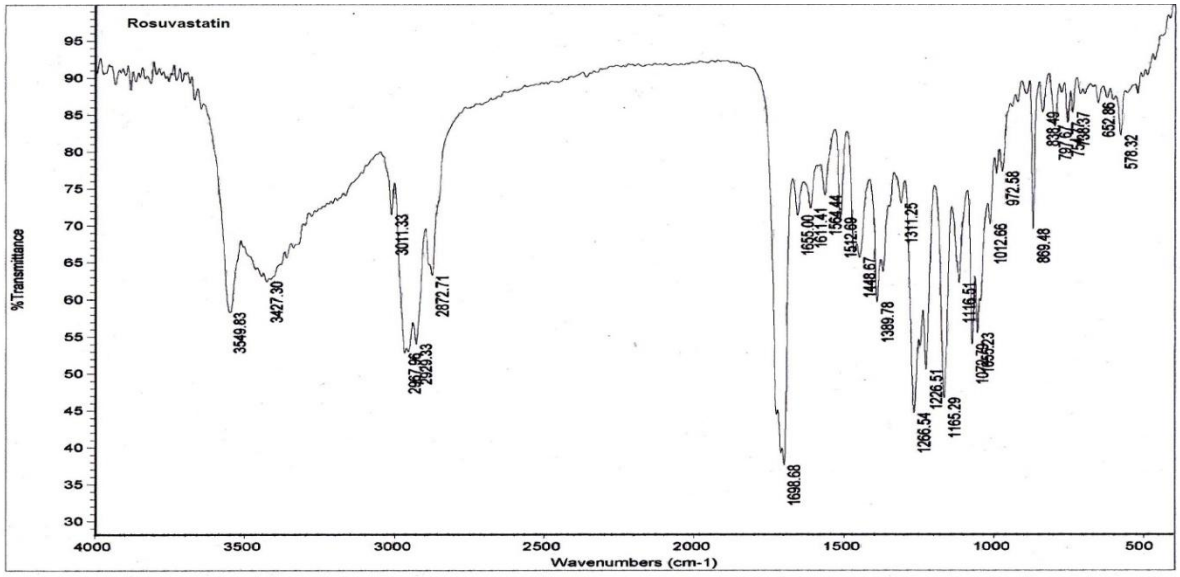

Fig No:5 FTIR Spectra of Rosuvastatin pure drug

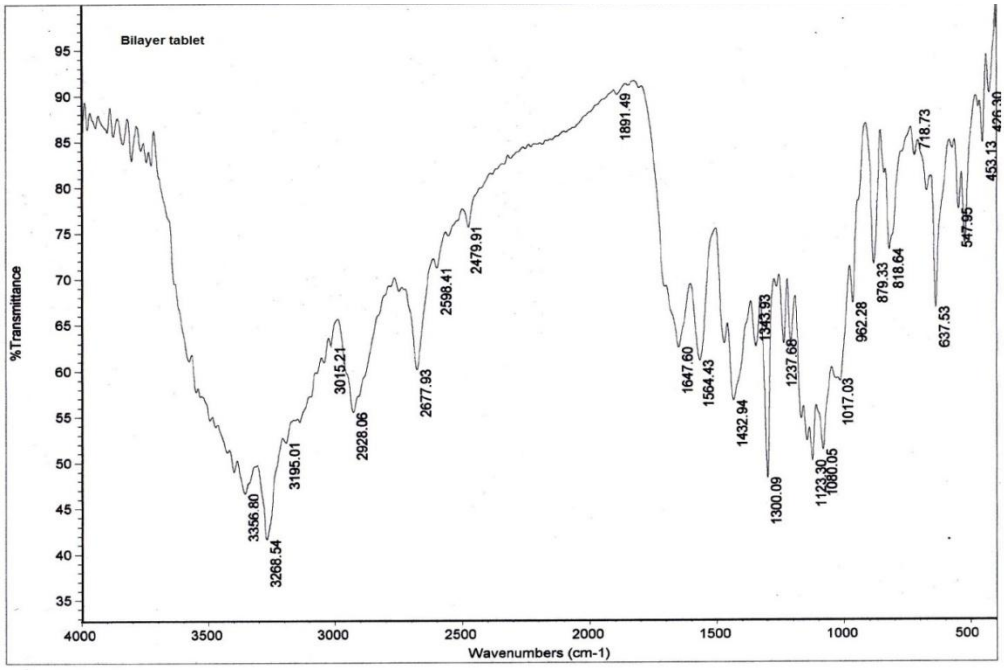

Fig No: 6 FTIR Spectra of Bilayer tablet formulation

Evaluation of pre compression parameters for sustained relaese layer of metformin

Table No- 6

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio
$F1_a$	26.3	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09
$F1_b$	27.4	0.322±0.045	0.376± 0.04	14.36±0.8	1.16±0.09
$F2_a$	25.8	0.423±0.044	0.322± 0.09	14.32±0.8	1.16±0.08
$F2_b$	25.3	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08
F3a	28.9	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08
F3b	24.7	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04
F4a	28.6	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09
$F4_b$	28.9	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08

From the above pre-compression parameters it was clear evidence that granules has excellent flow properties.

Tablet No -7: Post Compression Parameters for Sustained Release Tablet

F.CODE	*Hardness (kg/cm^2)*	Thickness (mm)	Friability (%)	Weight variation
$F1_a$	8.5	4.65	0.24	**952**
$F1_b$	8.3	4.47	0.25	**951**
$F2_a$	8.0	4.87	0.35	**954**
$F2_b$	7.4	5.33	0.56	**948**
F3a	7.6	5.84	0.45	**950**
F3b	7.9	5.5	0.25	**952**

F4a	8.2	5.6	0.21	**950**
$F4_b$	8.4	5.9	0.3	**954**

Invitro dissolution studies for sr tablets -

Dissolution study (sr tablets)

Acidic Stage

Medium : 0.1N HCL
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Temperature : 37°C± 0.5
Time : 2hrs

Buffer Stage

Medium : 6.8pH phosphate buffer
Type of apparatus : USP - II (paddle type)
RPM : 50
Volume : 900ml
Time : 8hrs

In vitro dissolution for SR tablets were done initially in 0.1N HCL for 2hrs and next in 6.8 phosphate buffer for 12hrs

In-Vitro Drug Release Studies for SR tablets

Table: 8cumulative percentage drug release of sustained layer

Time(hrs)	F1a	F1b	F2a	F2b
Dissolution medium 0.1N HCL				
1	45.8	9.45	30.18	16.09
2	69.18	18.0	45.0	28.63
6.8pH phosphate buffer				
3	82.54	27.90	69.0	39.36
4	86.81	49.63	70.72	50.54
5	100.21	73.82	89.61	68.6
6	--	98.61	100.21	81.81
7	--	--	--	100.2
8	--	--	--	--
9	--	--	--	--
10	--	--	--	--
11	--	--	--	--
12	--	--	--	--

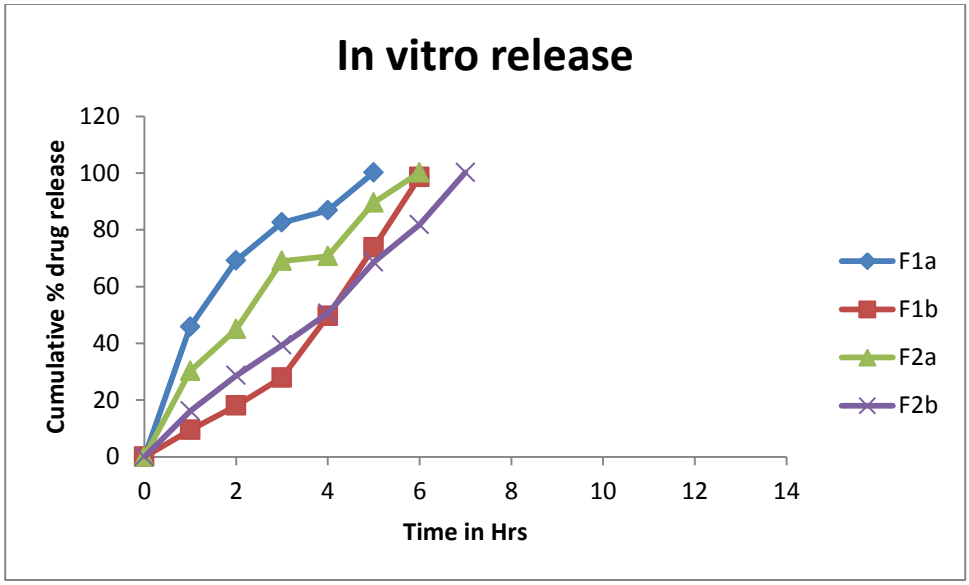

Fig no: 7dissolution graph for sustained release formulations

Table: 9 cumulative percentage drug release of sustained layer

Time(hrs)	F3a	F3b	F4a	F4b
	Dissolution medium 0.1N HCL			
1	15.13	11.8	28.6	26.8
2	40.28	18.21	39.2	34.82
	6.8pH phosphate buffer			
3	60.61	25.4	57.30	48.10
4	71.21	38.60	68.2	54.2
5	84.50	47.5	80.6	60.81
6	100.8	54.8	100.1	67.81
7	--	66.15	--	73.21
8	--	78.29	--	79.61
9	--	89.61	--	84.21
10	--	100.71	--	90.11
11	--	--	--	94.13
12	--	--	--	100.80

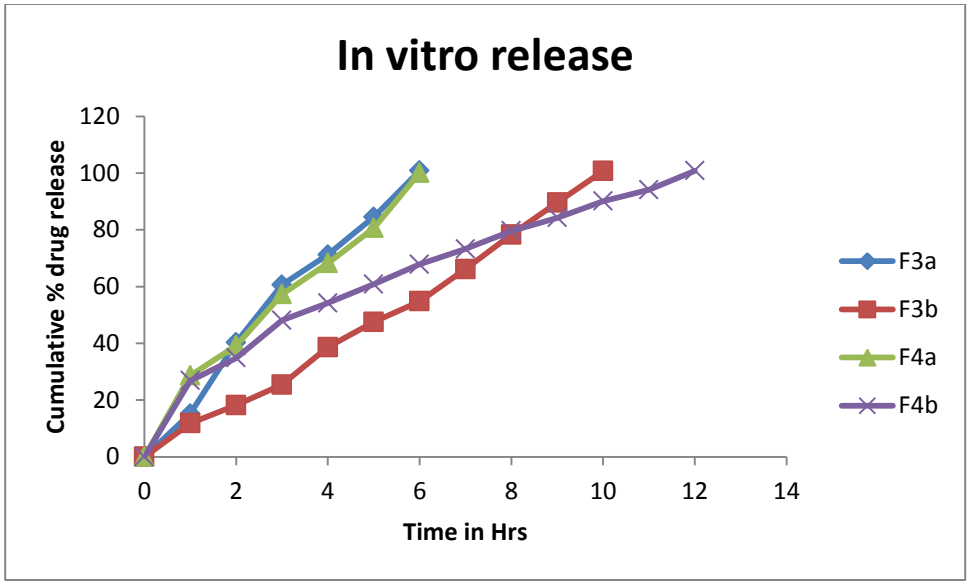

Fig No -8 dissolution graph for sustained release formulations

Release kinetics

Table no: 10 release kinetics for F4b formulation for sustained release layer

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log% Remain Vs T	% CDR Vs √T	Log C Vs Log T
Slope	7.330549451	-0.14919932	29.10473611	1.106423479
Intercept	18.67901099	2.192116307	-2.82112	0.924623948
Correlation	0.971501984	-0.88321131	0.998325682	0.781081855
R 2	0.943816105	0.780062226	0.996654168	0.610088865

EVALUATION PARAMETERS FOR IMMEDIATE RELEASE LAYER OF ROSUVASTATIN

Pre compression paramaetrs

Table No: 11 precompression parameters of ROSUVASTATIN

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	%Compressibility	Hausner's ratio
F1	24.6	0.276	0.322	14.28	1.16
F2	22.5	0.341	0.388	12.11	1.13
F3	24.8	0.324	0.376	13.82	1.16
F4	26.5	0.320	0.397	19.39	1.24
F5	22.1	0.521	0.629	17.17	1.20
F6	25.8	0.214	0.251	14.74	1.17
F7	23.6	0.308	0.364	15.38	1.18
F8	20.4	0.341	0.388	12.11	1.13
F9	24.1	0.320	0.397	19.39	1.24

Table No: 12: Post compression evaluation parameters for immediate release formulation

Physical parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	152	150	150	149	152	152	153	149	149
Hardness (Kg/cm^2)	6.3	6.5	6.4	6.8	5.9	5.0	6.4	6.8	6.5
Thickness (mm)	2.44	2.56	2.65	2.6	2.98	3.37	2.64	2.71	2.8
Friability %	0.4	0.5	0.3	0.25	0.36	0.48	0.47	0.50	0.45
Disintegration time	4mins 38 sec	fail	fail	2min 20 secs	4-5 secs	fail	5mins	9min	9secs

Table No 13: Dissolution for immediate release tablet of Rosuvastatin

Time	F1	F4	F5	F7	F8	F9
5	7.5	14.2	20.2	7.6	8.21	2 5.6
10	15.1	29.4	37.2	1 3.2	1 3.8	3 4.8
15	20.4	36.61	52.61	1 7.1	2 0.15	5 4.8
30	45.8	59.80	70.81	4 2.3	3 5.61	7 1.63
45	60.6	74.60	89.2	5 7.8	5 0.72	8 8.6
60	73.8	87.8	10 0.61	7 0.2	6 0.81	9 4.8

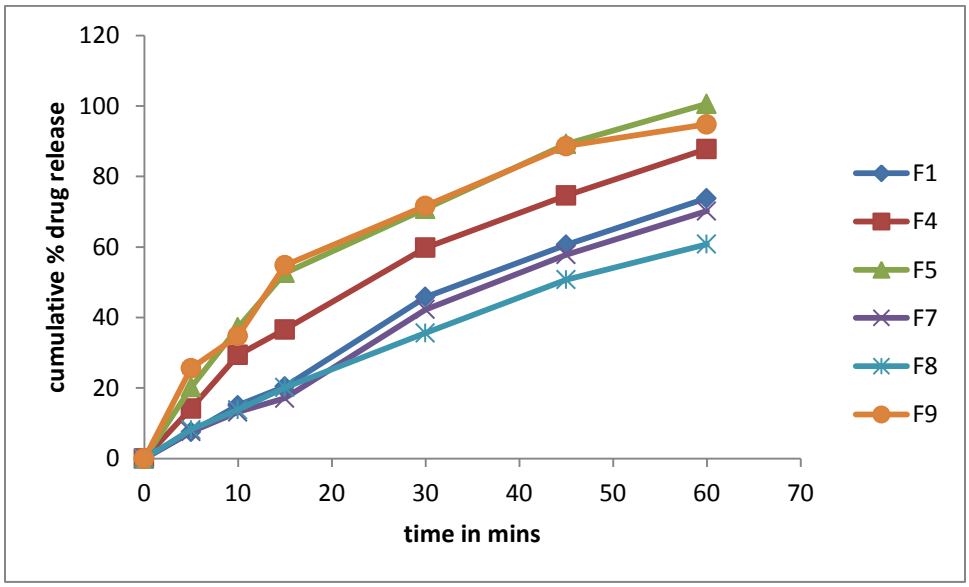

Figure No:9 Dissolution graph for formulations

BILAYERED TABLET COMPRESSION

After the batch was optimized in both immediate release layer (F5) and sustained release layer (F4b). The optimized batch in both was compressed by using same ingredients.

DISSOLUTION STUDY (BILAYERED TABLETS):

Dissolution Medium for IR tablets

Acidic Stage:

Medium	: 0.1N HCL
Type of apparatus	: USP - II (paddle type)
RPM	: 50
Volume	: 900ml
Temperature	: 37ºC± 0.5
Time	: 60min

In vitro dissolution for IR tablets were done in 0.1N HCL for 60 minutes.

Dissolution Medium for SR tablets

Acidic Stage

Medium	: 0.1N HCL
Type of apparatus	: USP - II (paddle type)
RPM	: 50
Volume	: 900ml
Temperature	: 37ºC± 0.5
Time	: 2hrs

In vitro dissolution for SR tablets were done in 6.8 pH for 12hrs.

Tab: 14 Dissolution profile of bi-layered tablet

		Percentage drug released (%)	
S.NO	**Sampling time**	**ROSUVASTATIN**	**METFORMIN**
1	**30mins**	**75.6**	**3.4**
2	**60 mins**	**99.8**	**8.4**
5	**1hr**	**--**	**27.2**
6	**2hr**	**--**	**35.9**
7	**3hr**	**--**	**49.2**
8	**4hr**	**--**	**56.8**
9	**5hr**	**--**	**63.7**
10	**6hr**	**--**	**69.2**
11	**8hr**	**--**	**83.6**
12	**12hr**	**--**	**99.4**

CONCLUSION

The F4b formulation which releases the Metformin in sustained manner in 1st hour it releases 26.58% but the remaining drug release was sustained up to 12 hours and Rosuvastatin immediate release F5 formulation showed 100.61 % drug release within 60 min.

With the data of kinetic analysis, F4b formulation showed best linearity in Higuchi's Equation plot indicating that the release of drug from matrix tablet follows Non Fickian diffusion.The dissolution study was carried out for optimized bilayer tablet and it correlates with the drug release of individual release layer formulations.

"Hence it may be summarized that the tablets prepared by direct compression method for sustained release layer and immediate release layer might be a perfect and effective formulation for poly therapy".

REFERENCES

[1]. Reynolds JEF, In; Martindale; The Extra Pharmacopoeia, 29th Edn., The Royal Pharmaceutical Society of Great Britain, London,1993, pp 295.

[2]. Mcnaman JO, Hardman JG, Limbird LE, Molinoff PB and Ruddon RW. Eds., The Pharmacological Basis of Therapeutics: 9th Edn. Mc Graw-Hill.

[3]. Indian Pharmacopoeia. Vol. II, 4th ed. TheController of Publications, New Delhi,1996, p736
[4]. AM Raggi; R Mandrioli; A Ferranti; J. Pharm. Biomed. Analysis., 2003, 32, 1037-1044.
[5]. J Siepmann; H Kranz; R Bodmeier; NA Peppas; Pharm Res., 1999, 16, 1748-1756.
[6]. Martindale: Thirty first Edition, The Complete Drug Reference. P.102.1
[7]. Chien YW. Controlled and Modulated Release Drug Delivery System in Swarbrik J, Boylan JC (Eds.). Encyclopaedia of Pharmaceutical Technology, Marcel Dekker, New York, 1990: 281-313.
[8]. Grabowski SR. Principles of anatomy and physiology. 10th ed. New York:John Willey and Sons; 2002: 866-873.
[9]. Tripathi KD. Essentials of Medical Pharmacology, 2009, 6th Edition, pg 627-651.
[10]. E Rippe. Compression of solids and compressed dosage forms. In: Encyclopedia of
[11]. Pharmaceutical Technology, third Edition, Swarbrick J. Marcel Dekker. Inc. NY, 1990: 149-166.